EHCJLI/04/03
MDSPS: AA04271
Protocol 466-07

Informed Consent

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A Randomized, Controlled Study to Evaluate the Short Term Exposure to Smoke Constituents of an Electrically Heated Cigarette Smoking System with Menthol in Adult Smokers During Controlled Smoking

Principal Investigator: James C. Kisicki, M.D.
MDSPS Project No: AA04271

Giving false, incomplete, or misleading information about your medical history, including past and present usage of medications, could have very serious consequences for your well being. It is vitally important that a true and complete medical history is given.

Please read this form carefully and do not hesitate to ask the study physician any questions about this form and/or the information provided below.

A. INTRODUCTION/PURPOSE

You are being asked to participate in a research study evaluating the short-term exposure to the compounds that make up the smoke of a menthol and non-menthol electrically heated cigarette smoking system (EHCSS) in adult smokers during confined smoking. The electrically heated cigarette smoking system (EHCSS) is available for purchase in a limited market area. This evaluation will be conducted by measuring identified biomarkers from cigarette smoke constituents in blood and urine and from vital sign measurements. A biomarker is a biological substance or biological effect, which can be measured to evaluate a relationship between a foreign substance, such as cigarette smoke, to a body process.

This study is not intended to assess any medical treatment and thus alternative treatment is not appropriate and the only alternative to participating is not to participate. You will receive no medical benefit from your participation in this study. There are no costs to you for participating in the study. All study supplies and study procedures are provided to you at no cost.

B. STUDY DESCRIPTION

Selected biomarkers in the blood, urine, and from vital sign measurements will be analyzed throughout the study. Initially, up to 140 healthy cigarette-smoking male and female adult volunteers will be enrolled in the study.

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SCREENING VISIT:

Screening will take place within 28 days prior to the beginning of the study to determine eligibility for participation, and will include the following examinations. :

- **Medical history** including the use of prescription and over-the-counter medications.
- **Physical examination**, which may include blood pressure, temperature, heart rate, respirations per minute, height, and weight.
- **Electrocardiogram** (*ECG*), which is an evaluation of the electrical activity of the heart
- **Pulmonary Function Testing** (**PFT**), which is an assessment of the function of the lungs
- **Blood and urine specimen collection** for general health screening to detect any abnormalities of the liver, kidneys, or immune system (*such as infections and/or unknown health conditions*) that may pose a risk to the participant, as well as a screening for HIV, hepatitis B, hepatitis C, the presence of drugs of abuse (*Some drugs, particularly cannabis (marijuana), can be detected for several weeks.*), alcohol.
- A **pregnancy test** (*blood*) for all female study participants.
- A **carboxyhemoglobin blood test** (a test to verify that you are a smoker).
- A smoking history questionnaire will be completed.
- A **Fagerström Scale** (a questionnaire that evaluates smoking habits) will be conducted.

CLINIC CONFINEMENT/GROUP ASSIGNMENT:

A detailed time-and-events schedule will be provided. The study covers one study period of 10½ days. You will be confined to the clinic during the entire study period.

You may smoke about the same number of cigarettes/day during the entire study that you reported as your normal smoking behavior at screening unless you are assigned to the No-smoking group. Group assignment will occur on Day 1. All subjects will continue to smoke Marlboro ULTRA LIGHTS Menthol prior to group assignment.

Check-in to the clinic will be the evening of Day-3. At the time of check-in, a medical/medication history and a brief physical examination including vital signs will be conducted. In addition, a blood and urine sample will be collected for clinical laboratory tests, which will include a serum pregnancy test for females and urine screen for alcohol and drugs of abuse. In addition a blood sample will be drawn for a carboxyhemoglobin test to confirm that you are a smoker. You will be required to check-in all personal cigarettes to the study staff. You will also be required to complete a diet and consumption questionnaire. You will be allowed to smoke Marlboro ULTRA LIGHTS Menthol upon request to the study staff until 11 PM that evening.

On the morning of Day-2 beginning at 7 AM, your cigarette consumption will be monitored in order to determine the number of cigarettes per day you will be allowed during the study. A maximum amount you are allowed to smoke will be determined based on your normal smoking behavior. Beginning on Day-2, smoking will only be allowed at designated times from 7 AM through 11 PM and all cigarettes smoked will be documented by the study staff.

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On the morning of Day-1, you will continue to smoke Marlboro ULTRA LIGHTS Menthol at designated smoking times, divided over 3 periods throughout the day (see below), up to your daily allotment as determined from Day -2.

Beginning on Day 1, 100 of the original 140 subjects will then be assigned to one of the four groups. Those subjects that are not assigned to one of the four groups will be released from the study. There will be 20 subjects in groups I, III, and IV and 40 subjects in group II. You will participate within your assigned group for the remainder of the study (morning of Day 9). The four groups are as follows:

Group I	Marlboro ULTRA LIGHTS Menthol
Group II	ACCORD JLI Menthol EHCSS
Group III	ACCORD JLI EHCSS
Group IV	No-smoking

If you are assigned to Group I, you will be allowed to smoke Marlboro ULTRA LIGHTS Menthol cigarettes for the duration of the study up to your allotted number of cigarettes per day. If you are assigned to Group II or III (electrically heated cigarettes), you will be allowed to smoke your assigned brand in a special lighter that allows you to get 8 puffs per cigarette for the duration of the study up to your allotted number of cigarettes per day. This allotment will be divided over 3 periods during the day (7AM through 12 noon, 12 noon through 5 PM, and 5 PM through 11 PM). IF YOU ARE ASSIGNED TO GROUP IV, YOU WILL NOT BE ALLOWED TO SMOKE AT ALL FROM DAY 1 TO THE END OF THE STUDY (MORNING OF DAY 9).

During the study, you will never be required to smoke by the study staff. In addition, you may choose to quit smoking at any time. Subjects in the smoking groups who elect to quit smoking may do so and will continue in their assigned group and will finish the study according to that group's schedule. If you choose to smoke, you may smoke up to your daily allotment of cigarettes evenly divided over 3 periods throughout the day (see above) and a personal smoking schedule will be created based upon your daily cigarette allowance.

During the confinement period, a clinic menu will be served and will include meat and dairy products. No foods or beverages containing alcohol will be served. Caffeinated beverages will be allowed at specified meal times.

Engaging in strenuous exercise or activities during the confinement period will not be allowed.

On the morning of Day 8, or upon early termination, a physical examination, ECG, measurement of vital signs, measurement of weight, and collection of blood and urine samples for clinical laboratory tests will be performed.

You will be released from the clinic following completion of the last 24-hour urine collection on the morning of Day 9.

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Smoking Topography

Your puffing profile (topography) will be measured by a machine designed to collect this information (CreSSmicro Portable measurement machine). On Days -2 and –1 (all subjects), and on Days 1, 2, 3, 4, 5, 6, 7, and 8 (smoking groups only), you will be provided with a portable measurement machine and you will be required to use it while smoking your first cigarette of the day and the first cigarette after lunch.

Urine Collection

All urine voided will be collected throughout confinement beginning on the morning of Day -1 and concluding on the morning of Day 9. You will be asked to void at specified times during the study to start and end collection intervals. In order to ensure that all urine is collected, the restroom doors will be locked throughout the collection period. A member of the clinic staff will provide participants with a labeled collection container and will unlock the restroom door for participants each time they need to enter the restroom.

ETS (Environmental Tobacco Smoke) Measurement

During one day of the study, each group will be moved to a designated room for determination of air particle and carbon monoxide measurements. Only 20 of the 40 subjects from Group II will participate in this evaluation. On the day of measurement, you will be confined to the designated room beginning 15 minutes prior to the start of the measurement to establish background levels. No smoking will be allowed during this 15-minute interval. Then, over the next hour, if you are assigned to one of the smoking groups, you will be allowed to smoke one cigarette in the room while the measurements are taken.

Larynx Exam

If you are assigned to group II (ACCORD Menthol smokers) or group III (ACCORD smokers) you will receive an examination of your larynx (voice box) by an ENT (Ear, Nose and Throat) physician on Day-1 and Day 8. This examination will consist of the spraying of a local anesthetic (such as Cetacaine) into the back of your throat, and the physician visualizing your larynx with a small mirror.

Vital Signs/Weight

Vital sign measurements and weight measurements will be performed at specified times throughout the study. Smoking will be prohibited for at least 15 minutes prior to each vital signs measurement.

Cigarette Butt Collection

All cigarette butts (Marlboro ULTRA LIGHTS Menthol) and used cigarettes (ACCORD groups) will be collected throughout the study.

Questionnaires

Two different product assessment questionnaires will be conducted for Groups II and III, on Day 1 through Day 8.

C. BLOOD COLLECTION

In this study, blood samples will be collected for clinical laboratory tests at screening, check-in, and on Day 8 (including pregnancy testing for females) and for study-biomarker analysis on Days -1 through 8. It is anticipated that 21 venipunctures (insertion of needle into vein) will be required in this group for a total of approximately 215 mL (7.2 ounces) of blood. If necessary for safety evaluations, additional samples may be collected.

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D. POTENTIAL RISKS/SIDE EFFECTS OF STUDY PROCEDURES, AND MEDICATION:

If you are assigned to the No-smoking group (Group IV) you may experience nicotine withdrawal symptoms which may include cigarette craving, irritability, restlessness, depressed mood, increased appetite, and difficulty concentrating.

Potential adverse effects to lung function tests include shortness of breath and dizziness.

During the examination of the larynx, you may experience gagging, pain and general discomfort.

Since there is always the possibility that some unexpected adverse effect may develop in some persons participating in the procedures in this study, trained medical personnel are available at MDS Pharma Services to provide immediate medical attention.

Cigarette smoking during pregnancy is associated with increased risk of spontaneous abortion, low birth weight infants, and prenatal mortality. Therefore, pregnant women cannot participate in this study and women of childbearing potential must avoid becoming pregnant during the study. Nicotine passes freely into breast milk and a nursing child may receive nicotine from a smoking mother's milk with the possibility of causing harmful side effects to the child. Therefore, women who are nursing cannot participate in this study.

The risks involved in drawing blood include pain, discomfort, infection, bleeding and/or bruising at the puncture site, and fainting.

Any significant or new findings developed during the course of this research that may relate to an individual's willingness to continue participation will be provided in writing in a timely manner.

E. REQUIREMENTS AND INSTRUCTIONS

Participation in this study requires that:

- You are generally healthy as determined by medical history, physical examination, ECG, pulmonary function testing, and clinical laboratory tests unless deemed not clinically significant by the Investigator and/or Sponsor.
- You are an adult between 21 and 65 years of age (inclusive) and have a smoking history of manufactured menthol cigarettes of between 10 and 30 cigarettes per day for 12 months prior to study initiation.
- You have smoked Marlboro ULTRA LIGHTS Menthol as your exclusive brand for a minimum of 4 weeks prior to study initiation.
- You have not used any other nicotine-containing product other than manufactured cigarettes (including roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) within 4 weeks prior to study initiation.
- You are capable of understanding and willing to sign this Informed Consent Form.

The study physician will review your medical/medication history, clinical laboratory results, ECG, pulmonary function tests, and physically examine you to determine your eligibility for this study. Following review of screening procedures by the Investigator and/or the Sponsor, you will be declined entry into the study for the following reasons (the list is not all-inclusive):

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- You have a clinically significant history or evidence (findings from physical examination, clinical laboratory tests, pulmonary function tests, ECG, or vital signs) of abnormalities of body systems/body organs/disease that in the opinion of the Investigator would jeopardize your safety or impact the validity of the study results related to any of the following:
  - **Gastrointestinal** – related to the stomach/intestines and conditions such as bleeding ulcers, inflammatory bowel disease, etc.
  - **Renal** – related to the kidneys and conditions such as kidney stones, etc.
  - **Hepatic** – related to the liver and related conditions such as cirrhosis, hepatitis, jaundice, etc.
  - **Endocrine** – related to gland function such as diabetes, thyroid disorders, etc.
  - **Oncologic** – related to cancers.
  - **Pulmonary** – related to the lungs/breathing and conditions such as chronic obstructive pulmonary disease and tuberculosis, etc.
  - **Cardiovascular** – related to the heart and blood circulation system, including conditions such as heart attack, abnormal ECG, chest pain, and congestive heart failure, etc.
  - **Neurological** – related to the brain and spinal cord, and conditions such as epilepsy, stroke, multiple sclerosis, seizures, etc.
  - **Psychiatric** – related to the brain in terms of behavior/emotions such as depression, and addictions such as eating disorders, drug abuse, alcohol abuse, etc.
  - **Hematological** – related to the blood and conditions such as anemia, clotting disorders, etc.
  - **Immunological** – related to the immune system and conditions such as autoimmune diseases, AIDS, etc.
- You have any history (current or past) of congestive heart failure.
- You have an active fever of greater than 100.2°F at screening or at check-in.
- You have an acute (sudden onset) illness (e.g. upper respiratory infection, viral infection, etc.) requiring treatment within 2 weeks prior to study initiation.
- You have donated blood of one pint or more or received a whole blood or blood product transfusion within 30 days prior to study initiation.
- You have donated plasma within seven days prior to study initiation.
- You have diabetes mellitus that cannot be controlled by diet and exercise alone (i.e. requires treatment with prescription anti-diabetic medication or insulin therapy).
- You require treatment with prescription or over-the-counter bronchodilator medications (e.g. inhaled or oral β-agonists).
- You are currently taking an antibiotic for an acute infection.
- You have had an allergic reaction to local anesthetics (such as Cetacaine, Xylocaine, Novocaine, etc....)
- You have a history of alcohol and/or drug abuse within the 12 months prior to study initiation.
- You have participated in a previous clinical study for an investigational drug, device, or biological product within 30 days prior to the study.
- You have a positive urine screen for alcohol and/or drugs of abuse.
- You or a first-degree relative (parent, sibling, child) are a current or former employee of the tobacco industry.
- You or a first-degree relative are a current employee of MDS Pharma Services.

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- If female, you are pregnant or nursing, or intend to become pregnant from screening through completion of the study.
- Your carboxyhemoglobin level at screening or check-in indicates that you are not a smoker.
- You are considered a puffer (a smoker who draws smoke from the cigarette into the mouth and throat, but does not inhale.

Restrictions For the Study

- Do not consume any foods or beverages containing alcohol during the 48 hours prior to the study. Alcohol will also not be allowed during the study.
- Do not engage in strenuous exercise for 48 hours prior to the study. Strenuous exercise will also not be allowed during the study.
- Avoiding heterosexual intercourse is the only certain way to eliminate the possibility of pregnancy. Therefore, if you are a woman of childbearing potential (i.e., not surgically sterile by hysterectomy or tubal ligation at least 6 months prior to study participation or at least 2 years postmenopausal) and sexually active, you must agree to utilize one of the following methods of birth control: hormonal contraceptives (oral, transdermal patch, implant, or injection) consistently for at least 3 months prior to study initiation and agree to continue throughout the study; barrier contraceptives (condom with spermicide, diaphragm with spermicide), or IUD for 2 weeks prior to study and agree to continue throughout the study, or have a partner who has been vasectomized at least 6 months. **Females must also accept the risk that pregnancy might result even while using these methods of birth control.**

F. CONFIDENTIALITY

Information collected during the study will be confidential and retained by MDS Pharma Services and the study Sponsor. All of this information is subject to review by the appropriate staff and representatives on behalf of the Sponsor, the Institutional Review Board, and possibly regulatory authorities, for verification of clinical procedures and/or data. Your permission for this review of confidential information is granted by signing this document. For purposes of study reporting, volunteers will be identified by initials and numbers only. However, your name, address, telephone number, and an individual to contact in case of an emergency will be kept in the record of the study doctor at MDS Pharma Services in case you need to be contacted in the future about this study. Under certain circumstances, some medical results will be reported to health authorities where required by law or statute. The results of this study may be published without disclosing your identity.

G. ACKNOWLEDGMENT

I understand that:

- At the conclusion of the study, regardless of whether I have chosen to smoke or quit smoking during the study, MDS Pharma Services will pay me up to $3,700 by check for my participation if I complete the study. If I am not assigned to one of the 4 study groups, MDS Pharma Services will pay me up to $700.00 for my participation in this study. If for any reason I do not complete the study (dropped by the Investigator and/or Sponsor, study is discontinued by the Investigator and/or Sponsor, dropped for not following the directions/instructions of the study staff, or if I choose to discontinue), I will be paid on a prorated basis. No deductions for any state or federal withholding or any other similar taxes will be made, and I am solely responsible for reporting such payment on my state and federal tax return and for the payment of any taxes due for the receipt of these payments from MDS Pharma Services.
- To reduce the health effects of smoking, the best thing to do is to quit smoking.

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- Participating in this study does not make me an employee of the Sponsor or MDS Pharma Services.
- While involved in this study, I will have direct access to medical attention.
- It may be unsafe for me to leave the clinic before being examined by MDS Pharma Services medical personnel.
- If I become physically injured or ill as a direct result of participation in this research study, MDS Pharma Services will provide the medical treatment necessary to assist in my recovery from the injury or illness. There will be no charge to me for this care beyond what is covered by my health insurance. This agreement to provide free medical treatment does not include treatment for any illness or injury I might experience during the course of the study if the illness or injury is not the result of the research study. No compensation other than free medical treatment of the injury or illness will be provided.
- If I experience an adverse reaction or injury while participating in this research, I will contact MDS Pharma Services' 24-hour Nurse's Line by calling (402) 790-4742. If I wish to contact the physician in charge of this study, I will call Dr. James C. Kisicki at (402) 476-2811 or, if after 4:30 p.m. or on weekends, at (402) 438-5922. Since the physician may not always be immediately available, the 24-hour Nurse's Line should be utilized.
- Provision of medical treatment shall not be an admission by MDS Pharma Services, or the Sponsor that my injury or illness is study related.

H. CONSENT

I have read this written informed consent document and freely consent to participate in this study.

I understand:

- The nature of the study.
- That I am a voluntary subject.
- The physician in charge can remove me from the study without my consent, either because of my failure to follow the study requirements, or if the physician feels it is medically in my best interest.
- The study includes examinations, including blood examinations, to which I will be subjected.
- The Sponsor may stop the study, or discontinue my participation, at any time at its discretion.
- Procedures in this study may be associated with undesirable effects, some of which are not known.
- That I may choose to withdraw from the study at any time.
- That I may refuse to participate, or withdraw from participation, at any time without penalty or loss of benefits to which I am otherwise entitled (I may be paid for my participation on a prorated basis).
- That nothing contained in this informed consent waives any of my legal rights as a volunteer, nor does it release the Investigator, the Sponsor, MDS Pharma Services, or its agents from any liability for negligence.

I agree to adhere to the regulations and directions of the study as outlined. I have been told how long and by what methods the study will be carried out, and I have been reminded that I have the opportunity to ask further questions about the details and procedures of the study.

All my questions have been satisfactorily answered. I have received a signed and dated copy of this consent form.

If I have any further questions regarding my rights as a volunteer, I will contact Frank E. Landis Jr., J.D., of the MDS Pharma Services Institutional Review Board at 1-800-776-1716.

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If I have any further questions about the study, I will contact MDS Pharma Services' 24-hour Nurse's Line by calling **(402) 790-4742.**

I. CERTIFICATION

I certify that I am between 21 and 65 years of age, inclusive, and have no known existing undisclosed medical problems.

I certify that I understand and meet the requirements for study participation as outlined in Section E (Requirements and Instructions), and will adhere to instructions of the study staff during the course of the study.

My signature below certifies that I understand the research investigation discussed above.

If female, I certify that I am not pregnant and not nursing.

Witness my signature this _____ day of _____ 20 __

Print Name: _____ Signature: _____

Person Administering Informed Consent: _____ _____
(Print or Type) (Signature)

Date: _____ MDS Pharma Services ID No.: _____

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